REMARKS/ARGUMENTS

Claims 44-46 remain in this application. Claims 1-43 and 47 have been canceled.

Claim Rejections – 35 USC §112

Claims 44-46 and 48-58 stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Response:

(6.) Claim 44 has been amended to further define the relationship between step (b) and (c). The formation of a binding complex has been added to separate other types of reactions. Step (d) is now amended to include a specific binding complex of step (b), thus removing the confusion as to the substantial exclusion or the ambiguity of the additional biospecific ligand. As shown in Table 1 in Example 3, the method is limited to amount or numerical proportion of cells, fragments and debris. Applicant has amended accordingly.

Claim 53 has been amended accordingly.

Claim 56 has been canceled.

Claim Rejections – 35 USC §102

Claims 44-46, 48, 49, and 52-61 are rejected under 35 USC 102(e) as being anticipated by Terstappen et al. (U.S. Patent 6,365,362).

Response:

(7.) Claims 44-46,48,49 and 52-61 assess the amount of labeled malignant cells, and said labeled cell fragments, debris, or clusters in assessing malignancy. Terstappen et al. only intact carcinoma cells are considered as an indicator of disease. Terstappen et al does not incorporate the role of the debris or fragments. In fact, Terstappen et. al. teaches away from incorporating the analysis of debris with a description of a two stage method to ensure enrichment of target CTC while eliminating a substantial amount of "debris and other interfering substances prior to analysis" (see US63655362, column 7, lines 62-66). Clearly, Terstappen et al. does not appreciate the importance of debris, fragments, or clusters in the

monitoring of disease and considers them a hindrance in monitoring malignancy. Data demonstrating that the blood of patients with prostate cancer are comprised of intact cell and a variety of disintegrated cells due the apoptosis suggests that CTCs are undergoing apoptosis, necrosis and other types of damage to varying degrees (see page 29 line 28 to page 30, line 2). Accordingly, the present invention shows that analysis of CTCs alone does not provide sufficient information to assess the state of CTCs and thus the state of malignancy.

Example 5 provides data to show that with the analysis of CTC there are obvious CTC and suspect CTC, both of which provide relevant information. Therefore assessing both is important to improving monitoring of the disease. High ratios of obvious CTC to suspect CTC (or debris) indicate progression of the disease, but low ratios of obvious CTC to suspect CTC (or debris) are indicative of a decrease number of intact CTC and a possible response to treatment. The present invention appreciates that during early stage cancer the presence of damaged CTC may be indicative of an active immune system response (page 34, lines 3-4). This immune response is, in part, responsible for dramatic increases in debris during therapy, suggesting the breakdown of tumor cells and possibly the therapeutic effectiveness.

Applicant respectfully suggests that Terstappen et al incorporates ONLY intact cells and does not appreciate the increased sensitivity and specificity with the incorporation of debris, fragment or cluster analysis. The analyzing amounts of labeled malignant cells, fragments or debris for a change in the numerical proportions is a physical feature not described in Terstappen et al, but provided in the present invention.

Claim Rejections – 35 USC §103

Claims 50-51 are rejected under 35 USC 103(a) as being unpatentable over Terstappen et al. (US Patent 6,365,362) in view of Carbonari et al. (Detection and Characterization of Apoptotic Peripheral Blood Lymphocytes in Human Immunodeficiency Virus Infection and Cancer Chemotherapy by a Novel Flow Immunocytometric Method, Blood 83(5):1266-1277 (March 1, 1994)).

Response:

(8.) Terstappen et. al. teaches away from incorporating the analysis of debris by eliminating a substantial amount of "debris and other interfering substances prior to analysis" (see US63655362, column 7, lines 62-66) as discussed above.

Carbonari would be unable to have the clinical sensitivity to assess apoptosis or necrosis as it relates to malignancy and therefore the combination would not provide the same analysis. Carbonari's lack of sensitivity to detect apoptosis is exemplified on page 1275, second column, second paragraph where 1 in 3 patients were detected with apoptotic lymphocytes in peripheral blood. Further, Carbonari is unable to confirm lymphocytes, from degranulated granulocytes and immature leukocytes with similar characteristics, primarily because Carbonari is indirectly assessing debris through peculiar light scatter and is thus unable to provide the direct enumeration necessary for assessing changes to intact cell/debris proportions.

The present invention takes a more direct approach by selectively capturing targeted intact cell, debris and fragments and then directly assessing the proportions of each to monitor malignancy. Further as discussed on page 33 line 10 through page 34 line 3, tumor cell debris within a particular particle size (for example about 1-3 um or the size of platelets) has been observed in much larger amounts than intact cells. Enumeration, therefore, could constitute a separate and independent marker other than intact tumor cells alone, not possible with Carbonari's method or level of sensitivity. Monitoring disease, apoptosis, necrosis, or even mechanical damage in the present invention would be obtained directly and with better sensitivity.

Carbonari's analysis is limited to flow cytometry and as shown in Example 3 (page 26, lines 1-13 and page 27, lines 1-9) CTC detection by flow cytometry encompasses intact CTC as well as damaged CTC and CTC fragments. Therefore, Carbonari could not have recognized the separation of damaged CTC and consequently not been able to monitor malignancy through intact and debris enumeration or proportioning. The combination of Terstappen et al in view of Carbonari et al would not provide the necessary selectivity or classification necessary to detect clinically or potentially clinically important debris or fragments.

Finally since morphology is lost in CTC debris, detection can be done by flow cytometry provided the debris is stained for cytokeratin (see page 12, lines 13-15).

Carbonari would not recognize the problem of lost morphology and therefore Carbonari would not consider incorporation of an antibody specific for cytokeratin to enumerate both intact cells and debris.

Applicant has amended claims 50-51 to limit the second biospecific ligand to cytokeratin to provide novel physical features that further distinguish the present invention.

Claims 44-46, 48, 49 and 52-61 are rejected under 35 USC 103(a) as being unpatentable over Schmitz et al. (US Patent 6,190,870) in view of Liberti et al. (US Patent 5,200,084).

Response:

(9.) Terstappen et. al. teaches away from incorporating the analysis of debris by eliminating a substantial amount of "debris and other interfering substances prior to analysis" (see US63655362, column 7, lines 62-66) as discussed above.

Schmitz et al incorporates the use of an internal high gradient magnetic matrix of closely packed ferromagnetic spheres in direct contact with the sample to separate specific binding complex. Using this platform, intact cells are exposed to a greater possibility of mechanical damage as they are brought into contact with the matrix and therefore a skewed proportion of debris in the final analysis. Schmitz et al does not discuss and therefore appreciate the problem of mechanical debris, while the present invention includes an external high gradient system to specifically remove this possibility of error (see the present application page 13, lines 26-31).

Liberti et al teach a magnetic separation method that incorporates colloidal magnetic nanoparitcles. However, Liberti et al does not appreciate the non-specific interactions and the coating requirements necessary to reduce this non-specific affect to allow clinically-appropriate monitoring for malignancy (see present application page 13 lines 16-20 and page 13 lines 29-31). The present invention includes an improved method for coating the particles to markedly improve the level of coating and non-specific interaction (page 14, lines 1-3). The method improves upon Liberti et al by a 3-5 fold lower non-specific binding characteristic. The method incorporates the use of BSA coating using a high temperature coating step.

Applicant has amended independent claims 44, 53 and 59 to incorporate this characteristic and further distinguish the present invention from the prior art.

Claims 50 and 51 are rejected under 35 USC 103(a) as being unpatentable over Schmitz et al. (US Patent 6,190,870) in view of Liberti et al. (US Patent 5,200,084) as applied to claims 44-46, 48, 49 and 52-61 as being unpatentable over Schmitz et al. (US Patent 6,190,870) in view of Liberti et al. (US Patent 5,200,084)) and in further view of Carbonari et al. (Blood 83(5): 1266-1277 (March 1, 1994)).

Response:

(10.) As discussed above, Schmitz et al incorporates the use of an internal matrix, exposing intact cells to mechanical damage which could alter intact cell and debris proportions in assessing malignancy. Liberti et al., as discussed above, incorporates the use of particles that lack the improved coating necessary for reduced non-specific interactions and dependable monitoring of malignancy. As discussed above, Carbonari does not provide the level of sensitivity for detecting and characterizing malignant cell fragments and debris. The combination of these references would not provide all the physical features that are incorporated into the present invention for monitoring malignancy.

Applicant has amended independent claims 44, 53, and 59 to reflect this issues and better distinguish the present invention from the prior art.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully assert that the present application is now fully in condition for allowance, and such action is respectfully requested. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

The Commissioner is hereby authorized to charge the extension fee and any other fees which may be required by this paper to Deposit Account 10-0750 VTN5060USPCT2/TFV. Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/ VTN5060USPCT2/TFV.

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